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AN ELECTRODYNAMIC MODEL FOR DETERMINING THE DISTRIBUTION FUNCTION OF PARTICLES BY SIZE FOR BLOOD CELLS *IN VIVO*

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Abstract. This paper is devoted to construction of a mathematical model for determining the distribution function of blood cells by size. After considering the problem of light scattering on a spheroidizied particle with a multilayer structure and arbitrary oriented in space, the reflection coefficient of a plane wave from the biostructure model with a smoothly irregular structure has been found. This approach made it possible to construct a model of the said structure with several layers. Based upon the reflection of a Gaussian beam from this structure the distribution function of blood cells by size was obtained. Some methods such as the T-matrices apparatus, the Huygens – Fresnel transform, the Tikhonov's regularization were involved. The mathematical model proposed for the first time allowed theoretical calculation of the size distribution functions of spheroidizied particles simulating blood cells for the case *in vivo*.

Keywords: laser technology, Tikhonov's regularization method, T-matrices method, Huygens – Fresnel transform

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ЭЛЕКТРОДИНАМИЧЕСКАЯ МОДЕЛЬ ОПРЕДЕЛЕНИЯ ФУНКЦИИ РАСПРЕДЕЛЕНИЯ ЧАСТИЦ ПО РАЗМЕРАМ ДЛЯ КЛЕТОК КРОВИ *IN VIVO*

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Аннотация. Работа посвящена построению математической модели для определения функции распределения клеток крови по размерам. После рассмотрения задачи светорассеяния на сферулированной частице, обладающей многослойной структурой и произвольно ориентированной в пространстве, определен коэффициент отражения

плоской волны от модели биоструктуры с плавнонерегулярным строением. Такой подход позволил построить модель указанной структуры, имеющей несколько биослоев. Исходя из отражения гауссова пучка от этой структуры была смоделирована функция распределения частиц по размерам. Привлекались такие методы, как математический аппарат Т-матрицы, преобразование Гюйгенса – Френеля, метод регуляризации Тихонова. Предложенная впервые математическая модель позволила теоретически рассчитать функции распределения по размерам сферулированных частиц, имитирующих форменные элементы крови для случая *in vivo*.

Ключевые слова: лазерная технология, метод регуляризации Тихонова, метод Т-матриц, преобразование Гюйгенса – Френеля

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Introduction

Laser technologies have recently become indispensable for solving diverse problems in fields of science and technology ranging from physics and chemistry to medicine and biology. Laser technologies are increasingly used in medical diagnostics, therapy and surgery, and this direction undoubtedly holds immense promise for future applications.

Non-invasive methods, including, most notably, optical ones, are in great demand as they offer a range of benefits (relative safety, reduced injury rate and infection risks, etc.) for diagnosis and treatment of diseases. Blood tests measuring the size and shape of erythrocytes, as well as their deformability and aggregation ability, monitoring the glucose levels in human blood, measuring the capillary blood flow velocity are of great importance for medicine if they can be carried out rapidly and non-invasively.

Biological tissues are optically inhomogeneous absorbing media with the average refractive index exceeding the one for air. Notably, cell membranes, nuclei and organelles, such as mitochondria, as well as melanin granules in cells serve as the main dispersers in many biological tissues [1–3]. There is evidence that cellular structures become increasingly chaotic with increasing malignancy of tissue neoplasms; at the same time, the size of individual cellular nuclei increases relative to the average value, while the relative refractive index of the cytoplasmic/nuclear environment may also change [1].

Blood tests are a fundamental step taken in modern medical practice to diagnose various pathologies. In this regard, it is important to analyze the optical properties of the so-called blood corpuscles, which include erythrocytes, leukocytes and platelets (in the traditional sense). However, erythrocytes, or red blood cells, make up more than 99% of the hematocrit (the percentage of corpuscles in the total blood volume). As is well known, along with their transport function, erythrocytes constantly participate in maintaining the vital activity of the body as a whole. Accordingly, the systematic deviations in the state of the corpuscles making up the bulk of blood cells directly affect the vital processes in the body.

Researchers and doctors attribute a dominant role in the pathogenesis of a significant number of diseases, complications and pathological conditions to microcirculatory and hemorheological dysfunctions. The functional properties of erythrocytes often play a significant and sometimes decisive role in these pathologies [4].

Evidently, the erythrocyte has specific mechanical and geometric properties, as well as a refractive index. This naturally brings theoretical and practical attention towards the characteristic properties of erythrocytes. For example, it would be interesting to determine the sizes of erythrocytes, their aggregation properties, refractive indices, especially in cases of various pathological abnormalities of the hematopoietic system.

A standard detailed clinical blood test is regarded by modern scientists as an extremely informative indicator of the physiological processes occurring in healthy and diseased states. This diagnostic tool also includes measuring the width of the size distribution of erythrocytes. This indicator is included in the standard comprehensive blood panel, confirming the importance of the data on the size distribution of erythrocytes for clinical practice.

Rapid and precise measurements of the size distribution of blood corpuscles are crucial in some diseases, such as iron deficiency or sickle cell anemia, elliptocytosis, spherocytosis, etc. [5].

Thus, it is essential to develop effective and quick methods for finding the size distribution functions of spherical particles imitating blood corpuscles. The parameters of erythrocytes, in particular their sizes, can be determined based on light scattering [3].

Therefore, we believe that formulating and solving this problem as an optical one is promising for such major areas as biomedicine and biophysics.

It is apparent that the model to be constructed must have the following properties:

sufficiently informative;

modern but not excessively complex;

fast to apply, i.e., not requiring resource-intensive computations.

The goal of this study is to model the size distribution function of spherical particles.

The paper has the following structure. First, we consider the problem of light scattered by a *j*-spherical particle with a multilayered structure, arbitrarily oriented in space, taking into account multiple scattering.

Next, we determine the reflection coefficient of a plane wave by a model of biological tissue with a smooth irregular structure. This approach allows to construct a satisfactory model of the biological structure with several biolayers.

The reflection of a so-called Gaussian beam is considered within the model proposed. In the course of our analysis, we naturally turn to the question of modeling the size distribution function of spherical particles.

Matrix formulation of scattering for *j*-spherical particles

Most studies relying on Mie theory regard the erythrocyte as a homogeneous sphere with the volume equal to the average volume of the erythrocyte. The erythrocyte can be considered to be a homogeneous scatterer due to the peculiarities of its structure. This representation of the erythrocyte is an adequate and effective approach to solving many problems of biomedical optics. The assumption of the spherical shape of the cells makes it possible to correctly predict the value of the scattering cross section of erythrocytes [3]. The scattering phase function of erythrocytes can be successfully approximated within the framework of Mie theory [1, 3]. Furthermore, Mie theory is well applied to describing the single scattering of incident laser radiation if randomly oriented erythrocytes or whole blood are examined.

As noted above, it is quite common to construct models where the shape of the blood corpuscles is assumed to be spherical. Such an approximation yields satisfactory results for a range of problems, especially since red blood cells are easily deformed and do not constantly retain their biconvex disk shape.

We take the spherical model of the erythrocyte as a basis; the rest of the blood cells are described as spheres with concentric inclusions [3].

The problem of laser radiation scattered by an aggregate of multilayered particles, serving as a model of aggregates in the blood medium, is solved in accordance with rigorous theory of multiple scattering. Using T-matrices as a mathematical framework allows to relate the decomposition coefficients of two electromagnetic fields: that scattered by a model aggregate and that incident on it. The connection between the scattered fields is described within this framework by taking into account the multiple interactions between the elements of the aggregate.

The T-matrices of all the elements of the aggregate do not depend on incident radiation, if we consider scattering by spherical objects. In this case, they can be calculated in the local coordinate system associated with the center of the selected particle.

Let us give a finite expression for the two components of the scattered field $E_{scat(\theta)}$ and $E_{scat(\varphi)}$ in the far field (a detailed formulation can be found in [6]):

$$E_{scat(\theta)} \sim E_0 \frac{e^{ikr}}{-ikr} \sum_{n=1}^{\infty} \sum_{m=-n}^{n} \frac{(2n+1)}{n(n+1)} \left[a_{mn}^{j} \tau_n - b_{mn}^{j} \pi_n \right], \quad (1)$$

$$E_{scat(\phi)} \sim E_0 \frac{e^{ikr}}{-ikr} \sum_{n=1}^{\infty} \sum_{m=-n}^{n} \frac{(2n+1)}{n(n+1)} \left[a_{mn}^{j} \pi_n - b_{mn}^{j} \tau_n \right], \quad (2)$$

where E_0 is the amplitude of the wave scattered by a spherical particle; **r** is the radius vector; **k** is the wave vector; *m, n* are the harmonic numbers; θ is the angle of incidence of the laser beam relative to the *z* axis; φ is the polar angle; $\tau_n = \partial P_n(\cos\theta)/\partial\theta$, $\pi_n = P_n(\cos\theta)/(\sin\theta)$ are Legendre polynomials; the coefficients a_{mn}^{j}, b_{mn}^{j} were defined in [6].

Expressions for the magnetic field *H* can be obtained using conceptually similar reasoning.

The problem on light scattering by a multilayered sphere was solved involving the mathematical concept described in detail in [7].

Using expression (1) as the basis for the θ-component of the scattered radiation intensity, we write the following expression:

$$I_{scat(\phi)}(\rho,\lambda) = I_i \cdot \left| E_{scat(\phi)} \right|^2, \quad (3)$$

where I_i is the intensity of the incident radiant flux, ρ is the reduced radius of the particle ($\rho = kl$, *l* is the dimensional radius of the particle).

Reflection of a plane wave from a smooth irregular layer

Solving the problem on reflection of a plane wave from a smooth irregular layer (Fig. 1) imitating the model biological structure under consideration, we refine the expression for the reflection coefficient from a layer whose main characteristic is a slowly changing thickness. The mathematical model contains the following bio-layers (see Fig. 1):

ambient air (*1*) through which the laser beam passes;

surface layer of the dermis, the epidermis (*2*);

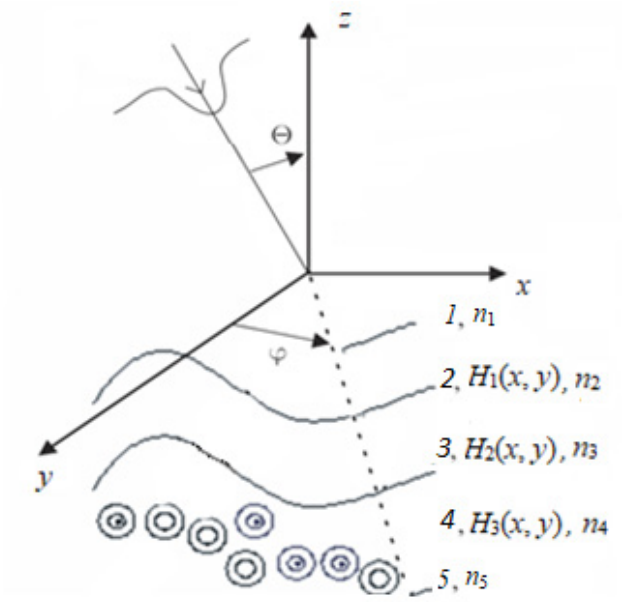

Fig. 1. Schematic representation of the model: laser radiation is incident on the biological structure, including layered components *2–5* between external environment *1* and lower dermis layers *5*: epidermis *2*, upper layers of dermis *3*, layer *4* with inclusions (aggregates of blood corpuscles); n_i is the refractive index of the *i*th layer

upper layer of the dermis (*3*);
layer consisting of spherical particles that imitate blood corpuscles (*4*);
lower layers of the dermis (*5*).

For the simulated model to best reproduce the real structure, the separation boundaries of the layers can be represented as wavy surfaces:

$$z_i = H_i(x, y),\ H_i = c_i \sin(\mathrm{a}_i x + b_i y), \tag{4}$$

where c_i, a_i, b_i are arbitrarily set constants, and $a_i \ll 1$, $b_i \ll 1$, $c_i \ll 1$, $i = \overline{1,3}$.

Let a plane *s*- or *p*-polarized wave fall on the modeled layer at an angle θ. For certainty, let us consider the case of *p*-polarization.

Reflected fields should be searched for as waves with rapidly oscillating phases and slowly varying amplitudes. The electrical components of the fields reflected from the 1st, 2nd and 3rd layers have the form

$$E_1 = \exp(\frac{i}{\varepsilon}\tau_{inc}(\xi_1, \xi_2, \xi_3)) + \exp(\frac{i}{\varepsilon}\tau_{1ref}(\xi_1, \xi_2, \xi_3))A, \tag{5}$$

$$E_2 = \exp(\frac{i}{\varepsilon}\tau_{2elap}(\xi_1, \xi_2, \xi_3))B^+ + \exp(\frac{i}{\varepsilon}\tau_{3ref}(\xi_1, \xi_2, \xi_3))B^-, \tag{6}$$

$$E_3 = \exp(\frac{i}{\varepsilon}\tau_{3elap}(\xi_1, \xi_2, \xi_3))C^+ + \exp(\frac{i}{\varepsilon}\tau_{3ref}(\xi_1, \xi_2, \xi_3))C^-, \tag{7}$$

and the components of the fields E_4 and E_5 are represented as follows:

$$E_4 = \exp(\frac{i}{\varepsilon}\tau_{4elap}(\xi_1, \xi_2, \xi_3))D^+ + \exp(\frac{i}{\varepsilon}\tau_{5ref}(\xi_1, \xi_2, \xi_3))D^- + E_{4scat\phi}(\xi_1, \xi_2, \xi_3), \tag{8}$$

$$E_5 = \exp(\frac{i}{\varepsilon}\tau_{5elap}(\xi_1, \xi_2, \xi_3))E, \tag{9}$$

where A, $B^{\pm}$, $C^{\pm}$, $D^{\pm}$ are the amplitudes; ε is a small parameter; $\xi_1 = \varepsilon x, \xi_2 = \varepsilon y, \xi_3 = \varepsilon z$ are the oblate spheroidal coordinates; $\tau_{inc}(\xi_1, \xi_2, \xi_3)$, $\tau_{1ref}(\xi_1, \xi_2, \xi_3)$, $\tau_{2elap}(\xi_1, \xi_2, \xi_3)$, $\tau_{3ref}(\xi_1, \xi_2, \xi_3)$, $\tau_{3ref}(\xi_1, \xi_2, \xi_3)$, $\tau_{3ref}(\xi_1, \xi_2, \xi_3)$, $\tau_{4elap}(\xi_1, \xi_2, \xi_3)$, $\tau_{5ref}(\xi_1, \xi_2, \xi_3)$ τ_{5elap} are the functions included in the eikonal equations for incident (*inc*), reflected (*ref*) and elapsed (*elap*) fields, respectively (the functions are defined in [8]).

Condition (8) contains a term $E_{4scat\phi}(\xi_1, \xi_2, \xi_3)$ that takes into account scattering (*scat*) in the 4th layer by inhomogeneities (spherical particles).

The next step is to find the amplitudes A, $B^{\pm}$, $C^{\pm}$, $D^{\pm}$. We write them as series in terms of degrees of the small parameter ε.

A recurrent system of equations for iterative determination of the terms in the series A, B, $C^{\pm}$, $D^{\pm}$ can be obtained by through standard continuity conditions for tangent components of electric and magnetic fields at the interfaces of the media, taking into account expressions (5)–(9). The reflection coefficient of the field can be obtained in the first approximation from the constructed system of equations.

Next, we need to find the reflected field for a Gaussian beam. To obtain the required field in the initial cross section (within the framework of the chosen method), we intend to apply the inverse transformation and then the Huygens–Fresnel integral transformation [8]. The number of primes in coordinate systems is of fundamental importance: the system (x', y', z') is associated with the incidence direction of the beam, and the system (x'', y'', z'') with the reflected field; the reflected field propagates along the line of the beam $z'' = 0$. The required field in the initial cross section is expressed as follows:

$$E_{ref} = \frac{A_{\widehat{00}}(\xi_1''^{\sim} + \xi_2''^{\sim}, k_{1y}, k_{1x})\Phi(\xi_1'', \xi_2'')}{\alpha} -$$
$$-\frac{\varepsilon_x}{\alpha}[A_{\widehat{01}}(\xi_1''^{\sim} + \xi_2''^{\sim}, k_{1y}, k_{1x}) + \frac{k_{13}}{kn_1}\xi_1'' A_{0000}(\xi_1''^{\sim} + \xi_2''^{\sim}, k_{1y}, k_{1x})]\Phi(\xi_1'', \xi_2'') -$$
$$-\frac{\varepsilon_y}{\alpha}[A_{\widehat{10}}(\xi_1''^{\sim} + \xi_2''^{\sim}, k_{1y}, k_{1x}) + \frac{k_{23}}{kn_1}\xi_2'' A_{0000}(\xi_1''^{\sim} + \xi_2''^{\sim}, k_{1y}, k_{1x})]\Phi(\xi_1'', \xi_2'') -$$
$$-\frac{\varepsilon_x\varepsilon_y}{\alpha}[A_{\widehat{11}}(\xi_1''^{\sim} + \xi_2''^{\sim}, k_{1y}, k_{1x}) + \frac{k_{13}}{kn_1}\xi_1'' A_{0000}(\xi_1''^{\sim} + \xi_2''^{\sim}, k_{1y}, k_{1x})]\Phi(\xi_1'', \xi_2'') - \quad (10)$$
$$-\frac{\varepsilon_x\varepsilon_y}{\alpha}[\frac{k_{23}}{kn_1}\xi_2'' A_{0000}(\xi_1''^{\sim} + \xi_2''^{\sim}, k_{1y}, k_{1x})]\Phi(\xi_1'', \xi_2'') -$$
$$-\{\frac{\varepsilon_x k_x^0}{ikn_1\alpha}[\frac{\partial A_{\widehat{00}}(\xi_1''^{\sim} + \xi_2''^{\sim}, k_{1y}, k_{1x})}{\partial k_{1x}} + \frac{\partial A_{\widehat{00}}(\xi_1''^{\sim} + \xi_2''^{\sim}, k_{1y}, k_{1x})}{\partial k_{1y}}]\frac{\partial\Phi(\xi_1'', \xi_2'')}{\partial\xi_1''}\} -$$
$$-\{\frac{\varepsilon_y k_y^0}{ikn_1\alpha}[\frac{\partial A_{\widehat{00}}(\xi_1''^{\sim} + \xi_2''^{\sim}, k_{1y}, k_{1x})}{\partial k_{1x}} + \frac{\partial A_{\widehat{00}}(\xi_1''^{\sim} + \xi_2''^{\sim}, k_{1y}, k_{1x})}{\partial k_{1y}}]\frac{\partial\Phi(\xi_1'', \xi_2'')}{\partial\xi_2''}\} + O(\varepsilon^2),$$

where the formulas $kn_1x' = k_{11}x + k_{12}y + k_{13}z$, $kn_1y' = k_{21}x + k_{22}y + k_{23}z$, $kn_1z' = k_{31}x + k_{32}y + k_{33}z$, $k_{11} = kn_1a_{11}$, $k_{12} = kn_1a_{12}$, $k_{13} = kn_1a_{13}$, $k_{21} = kn_1a_{21}$, $k_{22} = kn_1a_{22}$, $k_{23} = kn_1a_{23}$, $k_{31} = kn_1a_{31}$, $k_{32} = kn_1a_{32}$, $k_{11} = kn_{33}a_{33}$, $a_{11} = \cos\varphi\cos\psi - \sin\varphi\cos\theta\sin\psi$, $a_{12} = -\sin\varphi\cos\psi - \cos\varphi\cos\theta\sin\psi$, $a_{13} = \sin\theta\sin\psi$, $a_{21} = \cos\varphi\sin\psi + \sin\varphi\cos\theta\cos\psi$, $a_{22} = -\sin\varphi\sin\psi + \cos\varphi\cos\theta\cos\psi$, $a_{23} = \sin\theta\cos\psi$, $a_{31} = \sin\varphi\sin\theta$, $a_{32} = \cos\varphi\sin\theta$, $a_{13} = \cos\theta$ relate the coordinate systems (x', y', z') and (x'', y'', z''). The Gaussian beam $\Phi(\xi_1'', \xi_2'')$ and the coefficients obtained from the recurrent system of equations for iterative determination of the terms in the series (the amplitudes $A_{\widehat{00}}$, $A_{\widehat{10}}$, $A_{\widehat{11}}$, A_{0000} are decomposed into these series in terms of degrees of the small parameter ε) were found in [6].

The particulars of the geometry associated with the boundaries constructed for the reflecting medium, the characteristic properties of the incident beam itself (the distribution of the field in a fixed cross section and the angle of incidence) affect certain parameters of the reflected field. The reflected field is represented as the main term and the additive correction of the asymptotics with respect to the small parameter with an error $O(\varepsilon^2)$.

Next, if we assume the parameters of the given system to be fixed, then the distortions in the field of the incident beam upon reflection can be assumed to depend on two predominant factors against the background of the others.

The first of these factors is represented in Eq. (10) by expressions in square brackets:

$$\frac{\varepsilon_x}{\alpha}[A_{\widehat{01}}(\xi_1''^{\sim} + \xi_2''^{\sim}, k_{1y}, k_{1x}) + \frac{k_{13}}{kn_1}\xi_1'' A_{0000}(\xi_1''^{\sim} + \xi_2''^{\sim}, k_{1y}, k_{1x})]\Phi(\xi_1'', \xi_2'') -$$
$$-\frac{\varepsilon_y}{\alpha}[A_{\widehat{10}}(\xi_1''^{\sim} + \xi_2''^{\sim}, k_{1y}, k_{1x}) + \frac{k_{23}}{kn_1}\xi_2'' A_{0000}(\xi_1''^{\sim} + \xi_2''^{\sim}, k_{1y}, k_{1x})]\Phi(\xi_1'', \xi_2'') -$$
$$-\frac{\varepsilon_x\varepsilon_y}{\alpha}[A_{\widehat{11}}(\xi_1''^{\sim} + \xi_2''^{\sim}, k_{1y}, k_{1x}) + \frac{k_{13}}{kn_1}\xi_1'' A_{0000}(\xi_1''^{\sim} + \xi_2''^{\sim}, k_{1y}, k_{1x})]\Phi(\xi_1'', \xi_2'') -$$
$$-\frac{\varepsilon_x\varepsilon_y}{\alpha}[\frac{k_{23}}{kn_1}\xi_2'' A_{0000}(\xi_1''^{\sim} + \xi_2''^{\sim}, k_{1y}, k_{1x})]\Phi(\xi_1'', \xi_2'').$$

The reflected field can be obtained here by multiplying the expression for the incident beam field by the local reflection coefficient of the plane wave with unit amplitude, incident on the medium at the same angle as the beam.

The expressions in curly brackets in Eq. (10) describe the transverse diffusion of the amplitude:

$$\{\frac{\varepsilon_x k_x^0}{ikn_1\alpha}[\frac{\partial A_{\widetilde{00}}(\xi_1''^{\sim}+\xi_2''^{\sim},k_{1y},k_{1x})}{\partial k_{1x}}+\frac{\partial A_{\widetilde{00}}(\xi_1''^{\sim}+\xi_2''^{\sim},k_{1y},k_{1x})}{\partial k_{1y}}]\frac{\partial\Phi(\xi_1'',\xi_2'')}{\partial\xi_1''}\}-$$
$$-\{\frac{\varepsilon_y k_y^0}{ikn_1\alpha}[\frac{\partial A_{\widetilde{00}}(\xi_1''^{\sim}+\xi_2''^{\sim},k_{1y},k_{1x})}{\partial k_{1x}}+\frac{\partial A_{\widetilde{00}}(\xi_1''^{\sim}+\xi_2''^{\sim},k_{1y},k_{1x})}{\partial k_{1y}}]\frac{\partial\Phi(\xi_1'',\xi_2'')}{\partial\xi_2''}\}.$$

A similar process occurs during reflection due to beam distortion (deviation from the propagation direction of the reflected beam). It seems reasonable to refer to the expressions in square brackets as the geometric factor, and to those in curly brackets as the diffuse factor.

Thus, we formulated the expressions for the reflected field of the Gaussian beam for the case of *p*-polarization. Such characteristics of the system as the beam angle and the refractive index of the reflecting layer were assumed to be arbitrary in the problem statement. These results are asymptotics with respect to the small parameter (whose meaning is the ratio of the characteristic scale of the variation in the body's boundary profile to the characteristic distance).

Notably, the formulas are not uniform with respect to the incidence angle parameter, but changing the other parameters produces the final result. Considering the process where the incidence angle increases within the given expression, we can observe that the additive corrections of the asymptotics begin to grow, pointing to a gradual increase in the distortion of the beam. The resulting formulas lose their meaning if the incidence angle is increased to 90°. In this case, the reflected field is scattered into a wide range of angles (is spread out in space). There are no solutions of the wave equation that would have the character of a localized beam in space propagating in a certain direction from the reflective surface. Consequently, the reflective formulas hold true within the angular range from 0° to 89°. According to our estimates, the error of the calculations obtained lies at the level of quadratic asymptotic terms. Similar reasoning can be used to obtain a reflected field for the magnetic component of the field.

Size distribution function of the spherical particles

Let us pose an inverse problem, where the intensity of light scattered by an aggregate of spherical particles is known. The latter are located in the layer and serve as a model of the aggregate of blood corpuscles (see expression (11)). Based on the known intensity measured with a certain error, we must find the size distribution of erythrocytes for the *in vivo* case.

The problem is formulated as follows:

Determine the size distribution function of blood corpuscles for the in vivo case.

The problem is solved by finding the reflected field $\mathbf{E}_{blood}$ in a layer consisting of spherical particles with various sizes and refractive coefficients. It is defined as follows:

$$\mathbf{E}_{blood}=\mathbf{E}_{ref}-\mathbf{E}_{skin},$$

where $\mathbf{E}_{ref}$, $\mathbf{E}_{skin}$ are, respectively, reflected fields from the entire modeled optical system and sequentially from the layers (epidermis, upper layer, dermis).

The intensity of the reflected field in a layer consisting of spherical particles is expressed as follows:

$$I_{blood}(\theta,\lambda)=\left|E_{blood\perp}\right|^2+\left|E_{blood\|}\right|^2, \tag{11}$$

where $E_{blood\perp}=E_{z(blood)}\cos\theta+E_{x(blood)}\sin\theta$, $E_{blood\|}=E_{z(blood)}\sin\theta-E_{x(blood)}\cos\theta$.

The components E_x and E_z follow the expressions

$$\frac{\partial E_{z(\text{blood})}}{\partial y}-\frac{\partial E_{y(\text{blood})}}{\partial z}=-i\omega\mu_0\mu_j H_{x(\text{blood})},\quad \frac{\partial E_{\text{x(blood)}}}{\partial z}-\frac{\partial E_{\text{z(blood)}}}{\partial x}=-i\omega\mu_0\mu_j H_{\text{y(blood)}}, \tag{12}$$

$$\frac{\partial E_{y(blood)}}{\partial x} - \frac{\partial E_{x(blood)}}{\partial y} = -i\omega\mu_0\mu_j H_{z(blood)}, \quad \frac{\partial E_{z(blood)}}{\partial y} - \frac{\partial E_{y(blood)}}{\partial z} = i\omega\varepsilon_0\varepsilon_j H_{x(blood)}, \tag{13}$$

$$\frac{\partial H_{x(blood)}}{\partial z} - \frac{\partial E_{z(blood)}}{\partial x} = -i\omega\varepsilon_0\mu_j E_{y(blood)}, \quad \frac{\partial H_{y(blood)}}{\partial x} - \frac{\partial H_{x(blood)}}{\partial y} = i\omega\varepsilon_0\varepsilon_j E_{z(blood)}, \tag{14}$$

where ε_0, F/m, is the dielectric constant; ε_j is the dielectric constant of the model medium for the jth layer; μ_0, G/m, is the magnetic constant; μ_j is the magnetic permeability of the model medium for the jth layer; ω, s^{-1}, is the angular frequency.

Eqs. (12)–(14) correspond to the system of Maxwell equations in the Cartesian coordinate system.

In this case, the inverse problem is described by the Fredholm linear integral equation of the first kind:

$$Au \equiv \int_{\rho\min}^{\rho\max} I_{scat(\theta)}(\rho,\lambda)u(\rho)d\rho = f(\lambda), \tag{15}$$

where A is the integral operator; $u(\rho)$ is the required distribution of cells over the reduced radii (sizes); $I_{scat(\theta)}(\rho,\lambda)$ is the intensity of the scattered field by a spherical multilayered particle over the angle θ, this is the kernel of the integral equation $f(\lambda) \equiv I_{blood}(\theta,\lambda)$, where $I_{blood}(\theta,\lambda)$ is the scattered light intensity determined by expression (11).

Suppose that the function $I_{scat(\theta)}(\rho,\lambda)$ is continuous in a rectangle $\Omega = ([c,d]\times[a,b])$, while $f(\lambda) \in L_{2[c,d]}$, so that $a \equiv \rho_{min}$, $b \equiv \rho_{max}$, $c \equiv \lambda_{min}$, $d \equiv \lambda_{max}$.

We assume that we know not the function f itself but some approximate value f_δ corresponding to the condition $\|f - f_\delta\|_{L_{2[c,d]}} \le \delta$. In the case where the function $u(\rho)$ is assumed to be smooth, we can choose $U = W^1_{p[a,b]}$ as the solution space.

In fact, instead of the function $I_{scat(\theta)}(\rho,\lambda)$, we assign the function $I_{hscat(\theta)}(\rho,\lambda)$. At the same time, the following conditions are satisfied:

$$\left\|I_{scat(\theta)}(\rho,\lambda) - I_{hscat(\theta)}(\rho,\lambda)\right\|_{L_2(\Omega)} \le h.$$

In this case, the restriction holds true:

$$\left\|A - A_h\right\|_{W_2^1 \to L_2} \le h,$$

where A_h is the approximation for the integral operator A whose accuracy h corresponds to the kernel $I_{hscat(\theta)}(\rho,\lambda)$ in the operator norm.

To numerically find the distribution $u(\rho)$, we apply the Tikhonov regularization method [9, 10], since the inversion of the operator A for the inverse problem is unstable for space $W^1_{p[a,b]}$ and the Tikhonov equation has the following form [9, 10]:

$$(A_h^* A_h + \alpha C)u^\alpha = A_h^* f,$$

where A_h is the transformation operator from space $W^1_{2[a,b]}$ to subspace $L_{2[c,d]}$; A^*_h is the transformation operator from subspace $L_{2[c,d]}$ to space $W^1_{2[a,b]}$ (conjugated to A_h); C is the operator whose matrix was defined in monograph [9].

This problem statement assumes that there is no information about the smoothness of the exact solution. In this case, the operator of the initial integral equation A_h can be assumed to be acting from space $L_{2[a,b]}$ to subspace $L_{2[c,d]}$.

Let us write out the smoothing functional for the case under consideration:

$$M^\alpha[u] = \left\|A_h u^\alpha - f_\delta\right\|^2_{L_{2[c,d]}} + \alpha\left\|u\right\|^2_{L_{2[c,d]}} \to \min. \tag{16}$$

Then the Tikhonov equation should be written as

$$(A_h^* A_h + \alpha E)u^\alpha = A_h^* f.$$

The function minimizing the functional u^α depends on the value of the regularization parameter α.

Results of numerical calculations for the model medium

Let us consider a model medium that has the characteristics presented in Table 1.

The parameter values for the interfaces between the layers are chosen so that the model is as close as possible to the real data on the form of the surface boundaries of the corresponding layer in the structure of a typical human dermis, and the wavelength is $\lambda = 633$ nm (the center of the He-Ne laser line).

Table 1

Characteristics adopted for the model medium

Parameter	Notation	Parameter value for layer *i*		
		(*2*)	(*3*)	(*4*)
Layer thickness, μm	d_l	65	565	90
Arbitrary constant	a_i	−0.0024	0.021	0.041
	b_i	0.0200	0.030	0.050
	c_i	0.010		
Refractive index (real part)	n_{0i}	1.50	1.40	1.35

Notes. 1. Arbitrarily given constants are represented by Eq. (4): $H_i = c_i \sin(a_i x + b_i y)$.
2. The refractive index of the ambient air $n_1 = 1{,}000$; $n_i = n_{0i} + i\chi_i$ for the *i*th layer of the model absorbing medium, it was assumed that $\chi_2 = \chi_3 = \chi_4 = \chi_5 = 10^{-5}$; $n_{05} = 1.40$.

Let us list the conditions imposed for problem on finding the size distribution function of blood corpuscles imitating erythrocytes. Firstly, the framework of the mathematical model constructed for the interaction of laser radiation with a biological structure containing a particle aggregate assumed that number of particles in the given aggregate was finite. Secondly, both the structures of the aggregate elements and the effects of multiple scattering were taken into account; at the same time, the geometric and optical characteristics of the scatterers were assumed to be given exactly.

Fig. 2 shows examples for the calculated intensity curves of laser radiation scattering as a function of wavelength (scattering spectra) by two groups of spherical multilayered particles for cases of varying degrees of aggregation.

Analyzing the obtained results, we reached the following conclusions:

the mathematical approach used in the paper and the software developed based on this approach make it possible to detect the processes of particle aggregation in the model medium for the *in vivo* case (Table 2, see also Fig. 3);

variation of structural characteristics of the given aggregate (variation in the distances between the elements) leads to variation in both the numerical values of the spectral characteristics (see Fig. 2), and the shape of the curves themselves (Fig. 3). This effect is due to the difference in the size of the cells, as well as their internal structures.

The regularization parameter can be selected within the software program we have developed. This process was carried out automatically at the predefined error levels of the integral equation kernel. To select the regularization parameter providing an optimal ratio between a priori information and experimental data, the following methods were used: *L*-curve, relative residual, quasi-optimality criterion and smoothing functional (Fig. 4).

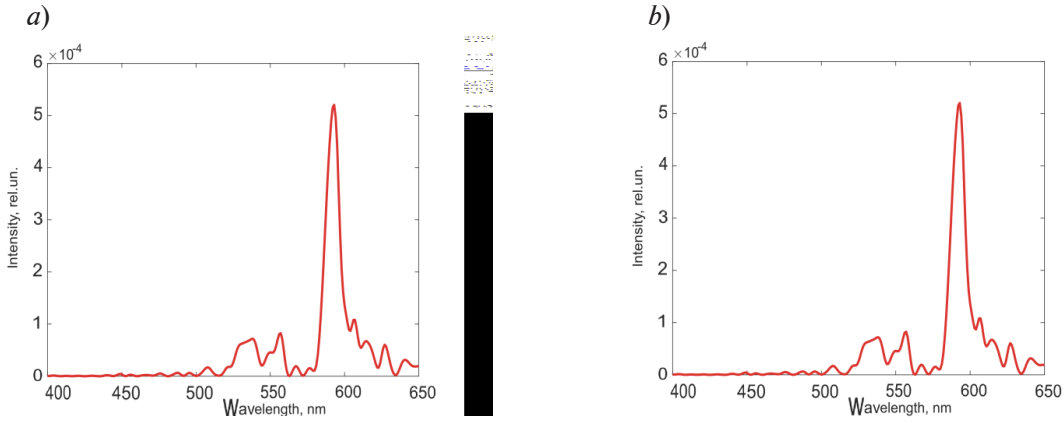

Fig. 2. Calculated intensities of laser radiation scattered by two groups each containing 5 spherical multilayered particles as function of radiation wavelength (incidence angle $\theta = 0°$); the distance between the particles was 1 μm (*a*) and 2 μm (*b*), the remaining parameters are given in Table 1.

Table 2

Size distribution function of particles obtained by simulation

Whole structure or structural element	Diameter, μm					Refractive index
Whole particle	6.5	6.5	7.0	7.6	8.0	–
Nucleus	4.0				3.0	1.37
Cytoplasm	5.0	6.0	6.5	6.5	4.0	1.00
Plasma membrane	–					1.33

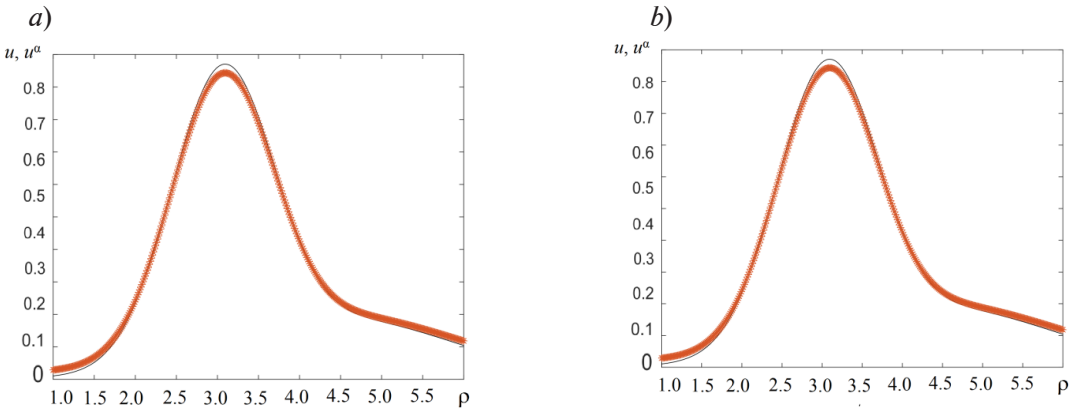

Fig. 3. Functions of bimodal (*a*) and normal (*b*) distributions of spherical multilayered particles over their reduced radii; the distances between the particles were 1 μm (*a*) and 2 μm (*b*). Thin lines correspond to the specified distributions, colored bold lines correspond to the calculated ones

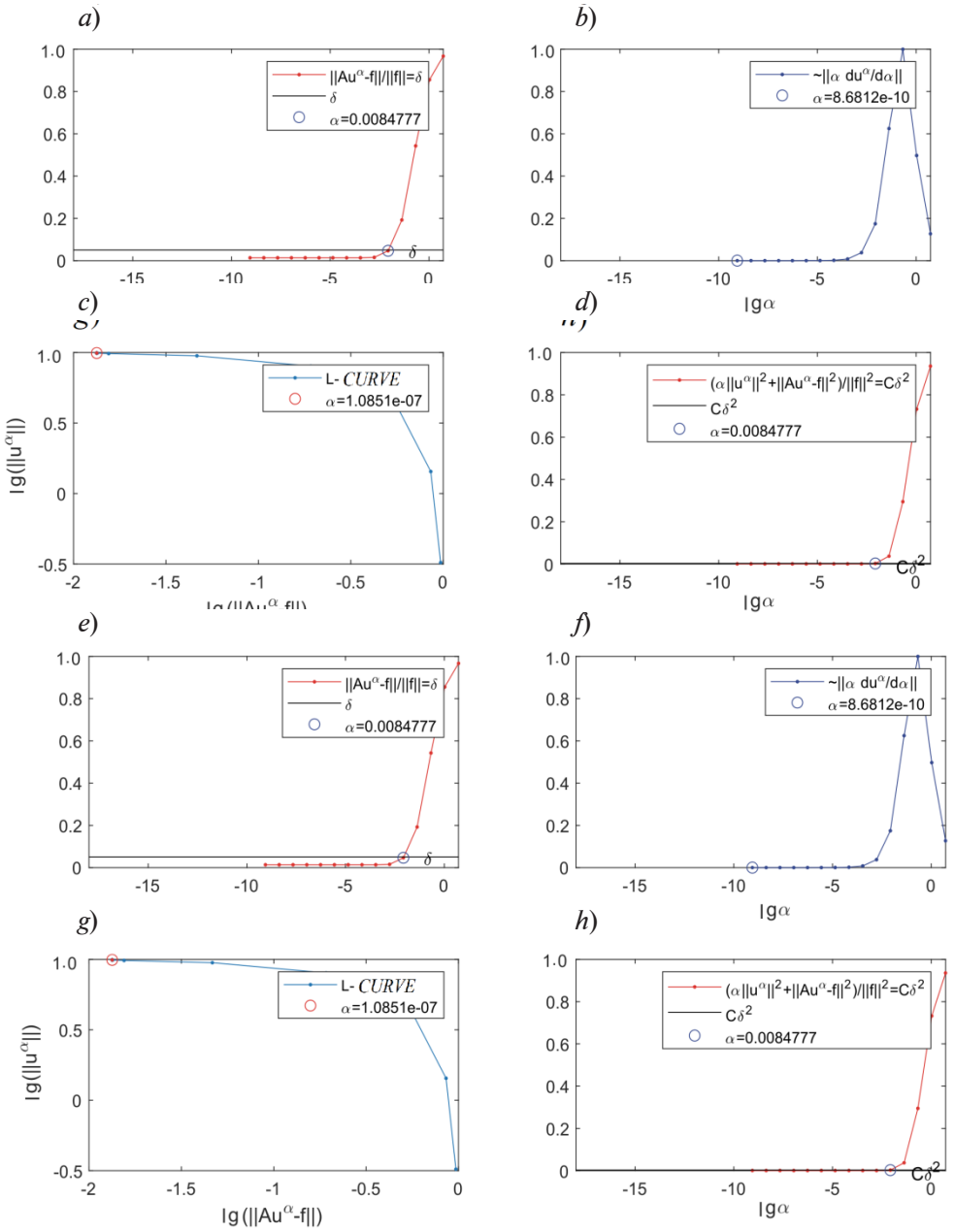

Fig. 4. Determination of regularization parameter for functions of bimodal (*a*–*d*) and normal (*e*–*h*) distributions of spherical multilayered particles using various selection methods: by relative discrepancy (*a*, *e*), by quasi-optimality criteria (*b*, *g*) and *L*-curve (*c*, *h*), as well as by the smoothing functional principle (*d*, *h*)

It seems reasonable to involve traditional data related to the size distribution of erythrocytes used in practical medicine to confirm the effectiveness of the above selection methods [11]:

$$u(\rho) = A_1 \cdot \exp B_1(\rho - b_1)^2, \tag{17}$$

$$u(\rho) = A_2 \cdot \exp B_2(\rho - b_2)^2 + A_3 \cdot \exp B_3(\rho - b_3)^2, \tag{18}$$

where A_i, B_i, b_i are fitting parameters.

The above equations (17) and (18) describe the normal and bimodal distributions, respectively.

The parameter values for a normal distribution are $b_1 = 2$, $A_1 = 1$, $B_1 = -2$, and $b_2 = 3$, $A_2 = 0.80$, $B_2 = -1.00$; $b_3 = 5$, $A_3 = 0.15$, $B_3 = -1.30$ for a bimodal distribution describing the case with the fraction containing 30% of abnormally large cells.

Let us consider the behavior of the two curves in Fig. 3,*a*. A predefined asymmetric bimodal size distribution of particles corresponds to a continuous curve simulating the presence of fractions of both abnormally large and normal formed elements (erythrocytes). Notably, the numerical solution of the problem allowed to reconstruct both the peak characterizing the fraction of normal cells and the peak corresponding to the fraction of abnormally large erythrocytes with a high degree of accuracy.

Similar interpretations can be given for the curves in Fig. 3,*b*. Here, the result of the numerical solution of the inverse problem is shown by a bold colored line (the noise level in the right-hand side of the equation is taken equal to 5%). The thin gray line corresponds to the size distribution function of particles based on relation (17). Evidently, the numerical solution of the problem given by relation (15) allowed to reconstruct the particle size distribution profile with high accuracy.

As a result, the constructed mathematical model makes it possible to theoretically calculate the size distribution function for spherical particles imitating blood cells for the *in vivo* case. We should also note that the solution obtained by minimization rather satisfactorily coincides with the predefined one for different types of distributions. It is significant that the error of the solution is commensurate with the noise level.

Conclusion

We can conclude from analysis of our findings that the new approach to describing the interaction of laser radiation with a layered medium, reproducing a model of biological tissue, has proved fruitful. The approach included asymptotic methods of diffraction theory. Let us briefly overview the main results obtained.

1. We formulated the expressions for calculating the reflected field of a Gaussian beam in the case of *p*-polarization of incident radiation, where such parameters as the incidence angle of the incoming beam and the refractive index of the reflecting surface are arbitrary. The formulas express the asymptotics with respect to a small parameter. The meaning of the small parameter introduced is the ratio of the characteristic variation scale of the body's boundary profile to the corresponding characteristic distance. The error of the calculations is of the order of quadratic asymptotic terms.

2. The constructed model satisfactorily reproduces the propagation of non-coagulating laser radiation into biological tissue with multilayered structure. This model allows to calculate the optical characteristics of the system, laying the foundations for qualitative analysis of the studied biophysical processes.

3. The mathematical model was constructed by means of the tools available in the software package, where the characteristic dimensions of the given biological structure can be freely varied in automatic mode. These advantages allow tracking the changes that occur when the input parameters are varied.

4. The new approach makes it possible to correctly reconstruct the distribution of red blood cells along the given radii taking into account the structural features of such a bioaggregate and accurately detect the changes in the distribution width of erythrocytes for the *in vivo* case.

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